

REMARKS

Claims 1-4 and 6-10 are currently pending. Claim 1 has been amended. Support for the amendment can be found throughout the specification, *e.g.*, page 30, lines 23-34. Claim 6 has been amended. Support for the amendment can be found throughout the specification, *e.g.*, Figure 3 and p. 31, line 30 to p. 32, line 10. Claims 11 and 12 are new. Support the new claims can be found in claim 6 as filed, as well as, in the specification, *e.g.*, page 31, line 30 to p. 33, line 30. No new matter has been added by way of these amendments. Furthermore, Applicants respectfully request entry of the amendments after final because the amendments cancel claims, place the claims into condition for allowance or in better form for consideration on appeal, and do not raise new issues for consideration in accordance with 37 C.F.R. § 1.116 and M.P.E.P. §§ 714.12 and 714.13. Therefore, entry of the amendments is respectfully requested.

Interview

Applicants appreciate the Examiner's interview of March 3, 2004. In the interview, Applicants' representative and the Examiner discussed the rejections in the office action. Specifically, Applicant's representative and the Examiner discussed the rejections of the claims under 35 U.S.C. § 102 over Walt and under 35 U.S.C. § 103 over Walt in view of Lockhart. There was a discussion about the teachings of the Walt reference and discussion of characteristics of the present invention that potentially differ from that in Walt. However, Applicant's representative and the Examiner did not reach agreement regarding any of the rejections. Nonetheless, the Examiner's position regarding certain rejections is more clear. It is hoped that the comments and amendments submitted herein overcome these rejections.

Priority

The Examiner rejects Applicants' assertion of priority to Provisional Application filed February 9, 1999 because the provisional application does not provide adequate support under 35 U.S.C. § 112 for the instant claims. Applicants disagree with this position for the reasons of record. Furthermore, Applicants submit that the rejection is moot as the difference in priority claimed by Applicants and that proposed by the Examiner has no effect on any other rejections, *i.e.*, none of the cited references have an effective filing date between the priority date claimed and that proposed by the Examiner.

Rejection Under 35 U.S.C. § 102

Claims 1-4 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Walt, *et al.* (USPN 6,327,410). In particular, the Examiner asserts that Walt teaches mapping a grid onto the first data image to create a registered first data image, contacting the random array with a sample, acquiring a

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second data image from the array to the sample, mapping a grid on the second data image to determine the presence or absence of the target analyte. Applicants respectfully traverse the rejection.

Anticipation of a claim requires that the reference teach every element of the claims. See M.P.E.P. § 2131. Thus, "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." See *Verdeegal Bros. v. Union Oil of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). It is imperative that the "identical invention be shown in complete detail as contained in the claim." See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Amended claim 1 (from which 2-4 depend) is directed to a method of determining the presence of a target analyte in a sample comprising acquiring a first data image of a random array composition, storing the first data image in a computer readable memory to generate a first stored data image, mapping a grid onto the first stored data image to create a registered first data image, contacting the random array composition with sample, acquiring a second data image from the array, storing the second data image in a computer readable memory to generate a second stored data image, mapping a grid onto the second stored data image to create a registered second data image, and comparing the first and second registered data images to determine the presence or absence of the target analyte.

Walt is directed to a microsphere-based analytical chemistry system and method for making the same in which microspheres or particles carrying bioactive agents may be combined randomly or in ordered fashion and dispersed on a substrate to form an array while maintaining the ability to identify the location of bioactive agents and particles within the array using an optically interrogatable, optical signature encoding scheme.

The present claims are distinguishable from Walt because the present claims require storing of data images in a computer readable memory to generate stored data images, mapping a grid over the stored data image, registering the data image, and comparing the first and second registered data image to determine the presence or absence of target analyte. The Examiner has not pointed to any teaching in the cited reference of a method that includes the use of a computer and manipulation of stored data images as presently claimed. Although figures 8 and 9 of Walt depict side-by-side comparisons of the camera-generated images to determine the change in optical signature, this is distinct from the method as claimed which require storing images in a computer memory, mapping a grid over the stored image to create a registering data images, and comparing the registered data images in the computer readable memory to determine the presence or absence of target analyte.

Based on the foregoing, Applicants submit that Walt does not each and every element of the claimed invention and respectfully request withdrawal of the rejection.

Claims 6-10 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Walt, *et al.* (USPN 6,327,410) in view of Lockhart, *et al.* (USPN 6,040,138). Specifically, the Examiner alleges that it would have been obvious to the skilled artisan "to apply the threshold measure of Lockhart *et al.* to the signal detection and comparison of Walt *et al.* to thereby determine the presence or absence of the bead, to discard a signal below the threshold and to accurately analyze and distinguish signals from background signals as taught by Lockhart *et al.*" Applicants respectfully traverse.

In rejecting claims under 35 USC § 103(a), the Patent Office bears the initial burden of establishing a *prima facie* case of obviousness. See M.P.E.P. § 2142; *see also In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993). To establish a *prima facie* case, three basic criteria must be met. First, the prior art must provide one of ordinary skill in the art with a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine their teachings. See *WMS Gaming Inc. v. Int'l Game Tech.*, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). The mere fact that references could be modified or combined does not render the resulting modification or combination obvious unless the prior art also suggests the desirability of the modification or combination. See *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). Second, the prior art must provide one of ordinary skill in the art with a reasonable expectation of success. The skilled artisan, in light of the teachings of the prior art, must have a reasonable expectation that the modification or combination suggested by the Examiner would be successful. See *In re Dow*, 5 USPQ2d 1529 (Fed. Cir. 1988). Third, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, and not in Applicants' disclosure. See *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). If any one of these criteria is not met, *prima facie* obviousness is not established.

Amended claim 6 (from which 7-10 depend) is directed to a method of signal pre-processing comprising acquiring a first data image of a random array composition and determining the similarity of a first signal from at least one discrete site to at least one reference signal, wherein the determination comprises obtaining the first signal from at least one discrete site and comparing the first signal to a threshold similarity measure obtained by comparing a reference signal to a theoretical signal, wherein when the first signal is within the threshold similarity measure, then the first discrete site contains a bead. The first signal is derived from signals obtained by measuring a first signal in first and second channels, said reference signal is derived from signals obtained by measuring said reference signal in said first and second channels and the theoretical signal is the signal expected to be obtained from a first signal when measured in first and second channels when no bleed-through occurs.

Applicants submit that the references, taken alone or in combination, do not teach or suggest the claimed invention. First, the Examiner cites Walt (at column 19, lines 31-35) as teaching the present invention. The Examiner alleges the cited passage to mean that Walt compares "a first signal to a second signal to determine bead presence which clearly suggests that they compare the signal to a threshold signal to determine the presence of the bead." The cited passage, however, discloses sequential loading of a library of microspheres, wherein the library is divided in a plurality of sublibraries. A sublibrary is placed on the array, the locations of the beads are determined based on optical signature, the second sublibrary is added, and the again the locations of the beads are determined. Walt states that by comparing the two *matrices*, the location of each bead in each sublibrary can be determined.

Second, Lockhart teaches comparison of absolute intensities of an array hybridized to nucleic acids from a test sample to a control sample provides a measure of the relative expression of the nucleic acids that hybridize to each of the probes. See Lockhart at column 23, lines 52-56. In situations where the nucleic acids are present at very low levels, the signal intensity may be very weak and indistinguishable from background. Thus, Lockhart suggests using a threshold intensity value below which the signal will not be counted. *Id.* at lines 63-67.

In contrast to both Walt and Lockhart and the combination of the two, the present invention compares a signal from a given bead with the threshold similarity measure to determine if the signal from that bead falls within the spectrum of what is considered to be the true signal for that specific optical signature. If it does fall within the threshold, then the bead is considered to express that particular signal. For example, if there is a strong signal, but it falls outside of the threshold similarity measure, the signal is not considered as the true signal for that specific optical signature. This allows a more confident determination of the bead given the bleed-through effect of fluorescence detection. See Specification at page 31, lines 24-33. The specification explains:

[W]hile in an ideal situation, each dye is highly specific and only gives a signal at a particular wavelength, the use of fluorescence in general and multiple "colors" in particular often results in a "bleed through" from one wavelength channel to another... Thus, any signal is analyzed by a plurality of measures or channels and the results obtained by the different measures or channels can contribute to a total signal or signature: a characteristic dye will give not only a characteristic signal, but also a characteristic bleed-through signature...

Id. Thus, a threshold similarity measure as taught in the specification is used as a means of more accurately determining whether the bead of interest is present. The threshold similarity measure is derived from a reference signal (measurement of the reference in the first and second channels) and a theoretical signal (the signal expected to be obtained from the signal of interest as measured in the first

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and second signals when no bleed-through occurs). The cited references do not teach the claimed threshold similarity measure that comprises a reference signal and a theoretical signal and comparison of the threshold similarity measure with a first signal as measured through first and second channels. Applicants submit that the cited references, taken alone or in combination, do not teach or suggest the use of a threshold similarity measure to account for bleed-through fluorescence in determining whether the bead of interest is present as presently claimed.

Even assuming, *arguendo*, that the references do teach the elements of the instant invention, Applicants submit that the cited references do not provide the requisite motivation to combine the references to render the instant invention obvious. The cited references seek to solve different problems that would not have been considered by those skilled in the art, at the time of filing and absent Applicants' disclosure, as being advantageous or even relevant for the alleged combination. Walt discloses a method of sequential loading to determine the location of a given bead within an array matrix. As shown in Figures 5 and 7 and described in the passages cited by the Office, a single bead fills each well of the array matrix. Thus, determination of bead loading is effectively binary such that each location either does or does not contain a bead. Walt does not indicate any dissatisfaction in the ability to distinguish sites having beads from those sites that are empty.

In contrast, The problem solved by Lockhart is determination of "hybridization signals that will vary with strength with efficiency of hybridization, the amount of label on the sample nucleic acid and the amount of particular nucleic acid in the sample." See Lockhart at column 23, lines 61-64. As a solution, Lockhart proposes a method to determine the expression level of a hybridization reaction using a threshold level to account for background noise. There is no suggestion in the art of record that the use of a threshold level for distinguishing varying signal intensities occurring in an expression experiment would be advantageous in the binary bead loading methods of Walt. Thus, those skilled in the art would not have been motivated to modify the satisfactory method of Walt.

Moreover, without the benefit of Applicants' teaching, the skilled artisan would not have had a reasonable expectation that the modification or combination suggested by the Examiner would be successful. In this regard, the threshold similarity measure of the instant invention is used to account for the bleed-through effect of optical signals and allows the user to determine whether the signal falls within the acceptable spectrum of what is considered the true optical signature of the coded bead. Even if the combination of the cited references would allow the quantification of signal intensity above background, the combination would not exclude signals that are a result of bleed-through fluorescence. In such a situation, the signal intensity would be above the threshold established in Lockhart and yet might not encode the correct optical signature. Accordingly, Applicants submit that the references would not have given one of ordinary skill in the art a reasonable expectation of success in practicing the claimed invention.

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Applicants submit that *prima facie* obviousness has not been established. The Examiner has not shown that the references, taken alone or in combination, teach or suggest the instant invention. As well, the Examiner has neither shown the requisite motivation to combine the references to render the instant invention obvious nor the likelihood of success of such a combination. Thus, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Final Office Action and, as such, the present application is in condition for allowance. Prompt and favorable consideration of this Amendment and Response is respectfully requested.

Please direct further questions in connection with this Application to the undersigned at (415) 781-1989.

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Customer Number: 32940
Dorsey & Whitney LLP
Four Embarcadero Center, Suite 3400
San Francisco, CA 94111-4187
Telephone: (415) 781-1989
Facsimile: (415) 398-3249

Respectfully submitted,
DORSEY & WHITNEY LLP

BY: David C. Foster

David C. Foster, Reg. No. 44,685 for
Robin M. Silva, Reg. No. 38,304
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